REMARKS/ARGUMENTS

Prior to this amendment, claims 181-183, 187, 189-191, 194-206 were pending. By the foregoing amendment, independent claim 181 has been amended to clarify the invention being claimed, dependent claims 182 has been cancelled in view of the amendments to claim 181, the language of dependent claims 190-191 has been clarified and new claim 207, directed to an elected invention, has been added. The amendments to claim 181 are fully supported in the specification, for example by Examples 1-9 and, on page 2, lines 31 to page 3, line 2; page10, lines 17-26; page 13, lines 13-34; page 16, lines 19-23; page 17, lines 17-23; and page 18, 14-30 No new matter has been added. Reconsideration is respectfully requested.

Specification Objection

In the Office Action, the specification was objected to on grounds that it contains a hyperlink or other executable code at page 12, line 5. Applicants thank the Examiner for the courtesy extended in identifying the hyperlink. The hyperlink has now been deleted from the specification. Applicants therefore respectfully request withdrawal of the objection.

Claim Objections

In the Office Action, claim 181 was objected to on grounds that it recites non-elected inventions. By the foregoing amendment, the list of Sequence ID numbers has been deleted from independent claim 181. New dependent claim 207 reciting Sequence ID number 2 (recited in original claim 184) directed to Applicants elected invention of Sequence ID #2 has been added.

Also in the Office Action, claim 191 was objected to. By the foregoing amendment, claim 191 has been corrected.

35 U.S.C. §103 Rejections

In the Office Action, all claims were rejected as being obvious over one or more of the Tjernberg et al., Garzon-Rodriguez et al., Goyal et al., Braun, Wolf et al., and Nordstedt et al. However, none of these cited references, taken alone or in combination, describes or renders

obvious the invention recited in Applicants' presently amended claims, for at least the reasons presented below.

Only *after* reading Applicant's disclosure would one of ordinary skill in the art even attempt to combine, modify and extend only certain selected teachings of the references, while ignoring other teachings of the references which teach away from and/or contrast with the present claims, to mechanically cobble together a facsimile of the present claims. Such hindsight reliance on applicant's claims and disclosure is an improper basis for rejecting the present claims. *W.L. Gore and Associates, Inc. v. Garlock, Inc.*, 721 F2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983).

As presently amended, independent claim 181 recites a composition comprising an isolated conformational epitope of a soluble amyloid aggregate which a) forms in a human or animal and b) contributes to amyloid disease, wherein the epitope is affixed to a curved or flat support surface to thereby constrain the epitope in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, and wherein the composition comprises a peptide and, wherein the support surface comprises a material selected from; gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

The Examiner states that Tjernberg et al. teaches that the polymerization of the amyloid fibrils results in the pathogenesis of amyloid diseases like Alzheimer's Disease, therefore is neurotoxic. Applicants do not dispute this statement, however, do not see its relevance to rendering the present invention obvious, which is directed to a composition comprising an isolated conformational epitope of a soluble amyloid aggregate which a) forms in a human or animal and b) contributes to amyloid disease, because nowhere in the disclosure does Tjernberg et al. disclose, teach or suggest such a composition wherein the epitope is affixed to a curved or flat support surface to thereby constrain the epitope in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, and, wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

The Examiner further alleges that Tjernberg et al. teaches conformationally constrained peptides in solution containing Aβ fragments necessary for aggregation and fibril formation. Tjernberg et al. in actual fact, concerns the design of peptides including variants of a decapeptide fragment of Aβ (previously shown to be one of the smallest peptides that includes a pentapeptide sequence necessary for Aβ-Aβ binding and aggregation and can form fibrils indistinguishable from those formed by full length Aβ) in order to determine which structural features are essential for fibril formation, and not soluble aggregate formation. Notably these fibrils are insoluble. In addition, the peptides of Tjernberg et al., are not designed for recognition by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, rather, they are designed for assembly of amyloid fibrils. The present composition comprises an epitope on the other hand, which is affixed to a support surface to thereby constrain it in a conformation that will allow, not for assembly into an insoluble amyloid fibril itself, but for recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril. As further stated in the specification on page 16, lines 19-23, the isolated conformational epitope is constrained by affixture to the support surface to allow for recognition by an antibody that binds an Aβ peptide aggregate, and not low molecular weight monomer, dimers, trimers or tetramers, or epitopes of mature amyloid fibrils or produced against amyloid deposits which comprise amyloid peptides aggregated into an insoluble mass.

Applicants submit therefore that Tjernberg et al. does not disclose, teach or suggest the epitope composition recited in claim 181. To the contrary, Tjernberg et al., by disclosing peptides that are specifically designed for assembly into insoluble fibrils, actually teaches away from the present invention as recited in claim 181, which is related to a composition comprising an isolated conformational epitope of a soluble amyloid aggregate. In addition, none of remaining references cure the deficiencies in the teachings of Tjernberg et al., either alone or in combination with Tjernberg et al. for at least the reasons presented below.

Garzon-Rodriguez et al. discloses that a conformational change in the carboxyl terminus of Aβ accompanies the transition from dimer to fibril. The Examiner alleges that Garzon-Rodriguez et al. teaches that the carboxy terminus is critical for the assembly dynamics of amyloid. The Examiner further alleges that it is well established that the amyloid fibrils are

formed by the sequential addition of Aβ subnuits, thereby teaching that amyloid peptides having epitopes for aggregate formation are bound to the amyloid fibril. Without disputing whether such conclusion is correct or in error, the present invention, as recited in independent claim 181, is not directed to a composition comprising an isolated conformational epitope comprising amyloid peptides having epitopes bound to the amyloid fibril. The present invention on the other hand, is directed to a composition comprising an isolated conformational epitope of an soluble amyloid aggregate, and not an amyloid fibril, where the epitope is affixed to a curved or flat support surface to thereby constrain the epitope in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, and, wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof, as recited by present claim 181.

Based on the above, the present invention as recited in independent claim 181 therefore, does not concern the assembly of an amyloid fibril. Furthermore, contrary to the teachings of Garzon-Rodriguez et al. wherein fibril formation in enabled by the presence of a free carboxyl terminus, dependent claims 195 and 196 which are directed to a conformational epitope composition comprising a peptide wherein a C-terminus is bound to the support surface, actually relate to disabling fibril assembly or formation using a C-terminus that is not free.

Based on the above, Garzon-Rodriguez et al. does not disclose teach or suggest the present invention as recited in claim 181, let alone any of the dependent claims which further limit claim 181 either directly or indirectly. In addition, Garzon-Rodriguez et al. does not cure the deficiencies in Tjernberg et al.

The Examiner states that Ingenito et al. teaches peptide synthesis by linking a thiol to generate peptide-C-terminal thioesters.

Applicants agree with the Examiner as to the teachings of Ingenito et al., but submit that Ingenito et al. does not disclose, teach or suggest the present invention, and even more importantly, does not cure the deficiencies in the teachings of Tjernberg et al. and Garzon-Rodriguez et al. as it pertains to independent claim 181, let alone any of the dependent claims, where the question of linking a thiol to generate peptide-C-terminal thioesters even arises.

The Examiner also alleges that Braun teaches the administration of pharmaceutical preparations or compositions comprising an antigen coated onto a surface of carrier particles of colloidal gold. The Examiner also alleges that since the particle is spherical, it would inherently have a curved surface.

The disclosure of Braun relates to adjuvants for vaccines. Braun discloses broadly that peptide adjuvants and antigen can be coated onto suitable carrier particles such as gold and tungsten. Braun does not specifically disclose, teach or suggest the present invention as recited in independent claim 181. In addition, Braun does not cure the deficiencies in the teachings of Tjernberg et al., Garzon-Rodriguez et al. and Ingenito et al., either taken alone or in combination. For example, Braun does not disclose, teach or suggest a composition comprising an isolated conformational epitope of a soluble amyloid aggregate, especially when the epitope is affixed to a curved or flat support surface to thereby constrain the epitope in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer of Aβ or an Aβ fibril, wherein the composition comprises a peptide, and wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

Goyal et al. discloses a method of determining the degree of aggregation of the βA4 peptide. Applicants submit that Goyal et al. does not disclose, teach or suggest the composition of claim 181 or cure the deficiencies in Tjernberg et al., Garzon-Rodriguez et al., Ingenito et al. and Braun, especially, for example, as it pertains to the epitope being affixed to a curved or flat support surface and wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

The Examiner alleges, based on Wolf et al., that it is well established in the literature that amyloid protein subunits associated with disease forming aggregates have a molecular weight of 4.2-4.5kDa.

Wolf et al. relates to the identification and characterization of C-terminal fragments of the β-amyloid precursor produced in cell culture. Wolf et al. does not disclose, teach or suggest the

presently claimed invention of claim 181, much less the dependent claims, and, does not cure the deficiencies in the teachings of Tjernberg et al., Garzon-Rodriguez et al., Ingenito et al., Braun and Goyal et al., especially, for example, as it pertains to a composition comprising an isolated conformational epitope of soluble amyloid aggregates, the epitope being affixed to a curved or flat support surface and wherein the support surface to thereby constrain it in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, wherein the composition comprises a peptide and wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

The Examiner alleges that Nordstedt et al. teaches the synthesis of ten-mers corresponding to consecutive sequences of Aβ 1-40 on a filter matrix, wherein the peptides are coupled to cellulose membranes using 2 molecules of β-alanine as spacer, i.e., the peptides are chemically bound to the membrane. The ten-mers disclosed by Norstedt et al. are actually 31 decapeptides, and not decameric aggregates of Aβ.

Furthermore, the disclosure of Nordstedt et al. pertains to compounds for the inhibition of polymerization of amyloid β peptide. Nordstedt et al. does not disclose, teach or suggest the presently claimed invention of claim 181, much less the dependent claims, and, does not cure the deficiencies in the teachings of Tjernberg et al., Garzon-Rodriguez et al. and Braun, especially, for example, as it pertains to a composition comprising an isolated conflormational epitope of soluble amyloid aggregates, the epitope being affixed to a curved or flat support surface and wherein the support surface to thereby constrain it in a conformation that will result in recognition of the epitope by an antibody that binds an Aβ peptide aggregate that is not a monomer, dimer, trimer or tetramer or an Aβ fibril, wherein the composition comprises a peptide, and wherein the support surface comprises a material selected from gold, zinc, cadmium, tin, titanium, silver, selenium, gallium, indium, arsenic, silicon, mixtures thereof and combinations thereof.

Based on the above, Applicants submit that none of the cited references, either alone or in any combination, describes, teaches or suggests a composition as recited in independent claim

181. Accordingly, the composition recited in independent claim 181, and even more so, the compositions of the presently pending dependent claims that further limit the composition of claim 181, are unobvious over all of the references cited in the Office Action.

Conclusion

For at least the above-stated reasons, Applicant believes all the pending claims are in condition for allowance and issuance of a notice of allowance is earnestly solicited. A three (3) month extension is hereby petitioned for pursuant to 37 C.F.R. 1.136. Payment of the fee due for such extension and for filing of the accompanying RCE is being made electronically at the time of filing of this response. However, the Commissioner is hereby authorized to deduct any underpayment, or to credit any overpayment, to Deposit Account No. 50-0878. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, the Examiner is invited to contact the undersigned at telephone (949) 450-1750.

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Respectfully submitted,

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